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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,491	12/05/2003	Jui H. Wang	11520.0338	9750

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/728,491	WANG ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25 and 32-34* is/are pending in the application.

4a) Of the above claim(s) *26-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25 and 32-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/04, 11/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 10-23-06.

Claims 1-34 are pending in the instant application.

Election/Restrictions

Claims 26-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10-23-06.

Applicant's election without traverse of Group I, claims 1-25 and 32-34, in the reply filed on 10-23-06 is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 7-12, 15, 18, 21, 24, 25, 32 and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to compositions and methods of inhibiting RIα/PKA expression in vitro and in vivo, and methods of inhibiting cancer cell growth in an individual comprising administration of any oligonucleotide between 21-30 nucleotides that comprises SEQ ID No. 1, or that has a one base mismatch with SEQ ID NO. 1, or any oligonucleotide between 18-30 nucleotides that comprises SEQ ID NO. 20 (which is a subsequence of SEQ ID NO. 1) or that has a one base mismatch with SEQ ID NO.20.

The specification and claims do not adequately describe the genus encompassing any oligonucleotide between 21-30 nucleotides that has a one base mismatch with SEQ ID NO. 1 (or SEQ ID NO. 20). This very broad genus encompasses a vast array of molecules, and the disclosure fails to provide a representative number of species for this very broad genus, and which are capable of inhibiting the expression of the RIα subunit of any protein kinase A in vitro or in vivo, and which further provides for the reduction of cancer cell growth in a subject.

The specification and claims do not adequately describe the concise structural features (e.g. polynucleotide sequences) that distinguish structures within the genus from those without. The specification teaches some (10) single base mismatches of SEQ ID NO. 1 and compares their success in target gene inhibition in vitro (table 2, p. 19 of the instant disclosure). One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus encompassing this vast array of oligonucleotides. Thus, one of skill in the art would reasonably conclude that Applicant was not in possession of the broadly claimed genus.

Claims 15-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting expression of human RIα/PKA in vitro comprising the administration of antisense oligonucleotides, does not reasonably provide enablement for inhibiting expression of any RIα/PKA in vivo, nor for reducing cancer cell growth in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to methods of inhibiting RIα/PKA expression in vitro and in vivo, and methods of inhibiting cancer cell growth in an individual comprising administration of any oligonucleotide between 21-30 nucleotides that comprises SEQ ID No. 1, or that has a one base mismatch with SEQ ID NO. 1, or any oligonucleotide between 18-30 nucleotides that comprises SEQ ID NO. 20 (which is a subsequence of SEQ ID NO. 1) or that has a one base mismatch with SEQ ID NO.20.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of nucleic acid treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of in vivo inhibition of target genes. (A. Branch, Trends in Biochem. Sci. 23:

45-50; *see* entire text for Branch; S. Crooke, Antisense Res. and Application, Chapter 1, pp. 1-50, especially at 34-36).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using nucleic acid based approaches Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (A. Peracchi et al, Rev. Med. Virol., 14: 47-64, especially at 51).

Agrawal et al also speak to the unpredictable nature of the nucleic acid based therapy field thus: "It is therefore appropriate to study each ... oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide (S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense." Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of nucleic acids in sufficient amounts to effect a phenotype or desired effect in vitro and in vivo (see Agrawal et al especially at pages 79-80; *see* Chirila et al., Biomaterials, 23: 321-342 in its entirety, especially at 326-327 for a general review of

the important and inordinately difficult challenges of the delivery of therapeutic nucleic acids to target cells).

See also the discussion by Opalinska et al of unpredictability of nucleic acid therapy, including the use of siRNA and antisense in vivo (Opalinska et al, Nature Rev., 1: 503-514, at 503 and 511). "Although conceptually elegant, the prospect of using nucleic-acid molecules for treating human malignancies and other diseases remains tantalizing, but uncertain... The main cause of this uncertainty is the apparent randomness with which these materials modulate the expression of their intended targets. It is a widely held view that molecule delivery, and selection of which messenger RNA sequence to physically target, are core stumbling blocks that hold up progress in the field. ...it is widely appreciated that the ability of nucleic-acid molecules to modify gene expression in vivo is quite variable, and therefore wanting in terms of reliability." [references omitted].

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting RIα/PKA in a subject, nor of reducing cancer cell growth in a subject comprising the administration of any oligonucleotides. The specification teaches some (10) single base mismatches of SEQ ID NO. 1 and compares their success with SEQ ID NO. 1 in target gene inhibition in vitro (table 2, p. 19 of the instant disclosure). This, however, is not representative of the ability to inhibit target gene expression in an organism, and further whereby treatment effects are provided by reducing cancer growth in that subject. The specification as filed fails to

provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery and the subsequent target gene inhibition comprising the administration by any means of a representative number of species of the genus of oligonucleotides claimed.

The breadth of the claims and the quantity of experimentation required. The claims are drawn to methods of inhibiting RIα/PKA expression in vitro and in vivo, and methods of inhibiting cancer cell growth in an individual comprising administration of any oligonucleotide between 21-30 nucleotides that comprises SEQ ID No. 1, or that has a one base mismatch with SEQ ID NO. 1, or any oligonucleotide between 18-30 nucleotides that comprises SEQ ID NO. 20 (which is a subsequence of SEQ ID NO. 1) or that has a one base mismatch with SEQ ID NO.20.

The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues whereby RIα/PKA expression is inhibited by a representative number of species of the genus of oligonucleotides claimed, and cancer cell growth in inhibited in a subject. Since the specification fails to provide sufficient guidance for the successful inhibition of target gene expression in vivo and cancer cell growth in inhibited upon administration of a representative number of oligonucleotides, it would require undue experimentation to practice the invention over the scope claimed.

Allowable Subject Matter

SEQ ID No. 1 appears free of the prior art searched and of record.

References made of record but distinguished from prior art

Zhou et al (WO 99/50409) teaches a 30-mer oligonucleotide comprising the complement of SEQ ID NO. 1 and SEQ ID NO. 20. Zhou does not qualify as prior art because the complement of this oligonucleotide is not taught (see SEQ ID NO. 8 of Zhou et al, whose alignment data is attached to the instant Office action).

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz, can be reached on (571) 272-0763. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose

telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
11-30-06